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(71)Applicant : SHIYUMEIDOU:KK

TOKAI KYOIKU SANGYO KK

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(72)Inventor : NAGANUSHI YOUICHIROU

IMANISHI YOSHIO

NAGATO YASUKAZU

TAKADA SHIGEO

SATO KIYOTAKA

(54) ANTI-MALIGNANT TUMOR AGENT USEFUL FOR CANCER SELECTED FROM
COLON CANCER, ESOPHAGUS CANCER AND BREAST CANCER

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain an anti-malignant tumor agent slight in adverse effect
and excellent in efficacy.SOLUTION: This anti-malignant tumor agent comprises a cyclic and straight- chain mixed
poly L-lactic acid having 3-19 degree of condensation as a main component which is a
fraction obtained by dehydrating and condensing L-lactic acid in a nitrogen gas atmosphere
by reduction in pressure and heating by stages to give a reaction solution, drying soluble
components of the reaction solution with ethanol and methanol under reduced pressure,
carrying out a reversed phase ODS column chromatography, eluting the adsorbed substance
with 25-50% aqueous solution of acetonitrile at pH2.0 and collecting a fraction prepared by
elution with 100% acetonitrile at pH2.0.

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CLAIMS

[Claim(s)]

[Claim 1] The anticancer drug used for the cancer which performed the opposite phase ODS column chromatography, used the mixed Pori L-lactic acid of the shape of annular [of 3-19], and a straight chain as the principal component whenever [condensation / which is the fraction eluted in 100% acetonitrile of pH2.0 after elution in 25 - 50% acetonitrile water solution of pH2.0], and was chosen from colon cancer, an esophagus cancer, and a breast cancer after carrying out dehydration condensation of the L-lactic acid according to gradual reduced pressure and temperature up in nitrogen-gas-atmosphere mind and carrying out reduced pressure drying of the obtained ethanol and methanol meltable component of reaction mixture.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to the anticancer drug used for the cancer chosen from the colon cancer, esophagus cancer, and breast cancer of an animal including people.

[0002]

[Description of the Prior Art] Although a surgical operation, a chemotherapy, and radiotherapy are the three major therapies of a malignant tumor conventionally, the actual condition is that still sufficient efforts are not bearing fruit. If it is in the chemotherapeutic drug by which pressure of business is carried out for a long period of time especially, not only a side effect is very strong generally, but the antitumor effectiveness is unfixed and a drug effective in solid cancers, such as colon cancer and an esophagus cancer, hardly exists.

[0003] For this reason, although it expects to heighten the antitumor effectiveness and various ** agent combination therapies are tried, duplication, enhancement, a new failure, phytotoxicity of a side effect, etc. were brought about, and remarkable deterioration of the quality (QOL) of life, compaction [exhausting / of physical strength] of a life by the therapy, etc. are generated not a little.

[0004] Although various immunotherapy is proposed as a new therapy over a malignant tumor, it is a research phase and waits for early implementation of an effective immunotherapy agent with few side effects.

[0005] The injection to a blood vessel, a neoplasm part, etc. is a subject also about a route of administration, and the actual condition of the anticancer drug for taking orally with high usefulness is [that there is nothing] equal. Moreover, L-lactic acid is heated in the ambient atmosphere of inert gas, such as nitrogen gas, under ordinary pressure or reduced pressure. [whether filtrate is melted to the acetonitrile after reduced pressure drying by filtering the obtained reaction mixture after the dissolution to a methanol or ethanol at the time of heat, and] Or the opposite phase system ODS or DS column which equilibrated beforehand the solution melted to the direct acetonitrile in 25% acetonitrile water solution of pH 2-3 performs a chromatography. In 30 - 50% acetonitrile water solution of pH 2-3, after elution, The malignant tumor cell proliferation inhibitor of an animal with which it is the fraction eluted in the water solution of 70% or more of acetonitrile concentration of pH 2-3, and whenever

[condensation.] contains those which whenever [L-lactic acid straight chain-like condensate / of 5-23 / and condensation] becomes from mixture with the L-lactic acid annular condensate of 2-15 as JP, 5-310581, A It is proposed. This thing was a thing to a man carcinoma-of-uterine-cervix stock cell, a man nasopharyngeal cancer stock cell, a man floor-of-mouth carcinoma cell line cell, a mouse lung cancer cell, a rabbit hepatic-carcinoma origin stock cell, Yoshida's sarcoma, people's gastric cancer, a thyroid cancer, lung cancer, and a uterine cancer.

[0006]

[Problem(s) to be Solved by the Invention] Whenever [condensation], this invention person showed the strong antitumor effectiveness to colon cancer, an esophagus cancer, and a breast cancer by having made inhibition of glycolysis activity with the Pori L-lactic acid of 3-19 remarkably increasing by the

malignant tumor into the main action mechanism, and discovered having the remarkable condition improvement operation including relaxation of the pain accompanied to a malignant tumor. It is the first anticancer drug to which tumor growth depressor effect is brought by interference to the metabolic system of a neoplasm, without being accompanied by the critical side effect.

[0007] This invention aims at offering the Pori L-lactic acid of 3-19 as an anticancer drug of an animal including people whenever [condensation / by which characteristic effectiveness was newly found out in this way].

[0008] This does not have a positive cure, to the overlooked very malignant neoplasm, creates a new cure and ** it to much more improvement in the rate of recovery according to concomitant use with the existing anticancer therapy etc.

[0009]

[Means for Solving the Problem] In order to attain the above-mentioned object, the anticancer drug of this invention Dehydration condensation of the L-lactic acid is carried out according to gradual reduced pressure and temperature up in nitrogen-gas-atmosphere mind. After carrying out reduced pressure drying of the obtained ethanol and methanol meltable component of reaction mixture, An opposite phase ODS column chromatography is performed. In 25 - 50% acetonitrile water solution of pH2.0 After elution, The mixed Pori L-lactic acid of the shape of annular [of 3-19] and a straight chain is used as a principal component whenever [condensation / which is the fraction eluted in 100% acetonitrile of pH2.0], and the anticancer drug used for the cancer chosen from colon cancer, an esophagus cancer, and a breast cancer is used.

[0010] Although Pori L-lactic acid consists of condensation products of the shape of annular and a straight chain, even if it compares with data, like that a kind of reversible equilibrium relation is materialized among both, and the antitumor effectiveness is discovered with compound of each fraction from which whenever [versatility / of the bioactive of Pori L-lactic acid / or condensation] differs, the meaning of carrying out mutual separation and using the condensation product of the shape of annular and a straight chain is scarce.

[0011] Separation purification of the Pori L-lactic acid of 3-19 is carried out whenever [condensation], and in order to present a actual activity, after carrying out alkali neutralization, use as original powder what carried out reduced pressure drying, and this is dissolved or suspended in sterile in a suitable solvent, and a vial bottle etc. is filled up with it so that it may become predetermined concentration, and let it be injections.

[0012] An oral agent mixes with a suitable dispersant, a basis, an allocated type agent, etc. said original powder processed similarly so that it may become predetermined concentration, and it pharmaceutical-preparation-izes it in the gestalt of powder material, a capsule, liquids and solutions, etc.

[0013]

[Example]

put 500ml of L-lactic acid into the separable flask stored in the example mantle heater of manufacture, perform 300ml inflow for /and of nitrogen gas, and churning, and ***** should pass the top-down communication trunk which kept it warm -- while leading to a flask with a reflux condenser -- 145 degrees C -- 3 hours -- heating -- further -- after decompressing to 150mmHg(s) and heating for 3 hours, at 155 degrees C of 3mmHg, it heated at 185 degrees C of 3mmHg(s) at the last for 1.5 hours, and the Pori L-lactic acid which is a resultant was obtained for 3 hours.

[0014] after keeping the obtained Pori L-lactic acid at 100 degrees C and dropping methanol 400ml following ethanol 100ml, respectively -- cooling radiationally -- this -- further -- methanol 500ml -- it agitated [be / it / under adding] well, and after putting, it filtered and refined and reduced pressure drying of the filtrate was carried out, it dissolved in the acetonitrile and the whole quantity was set to 200ml (undiluted solution).

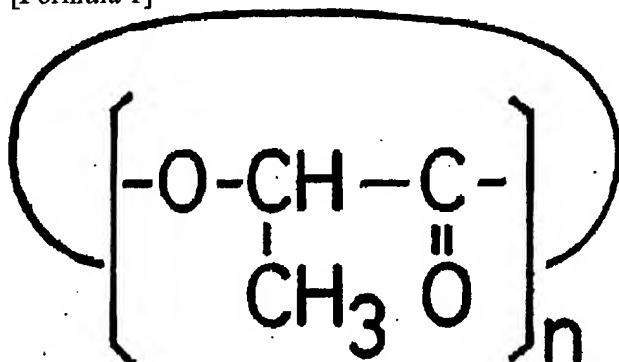
[0015] The aforementioned undiluted solution was covered over the opposite phase ODS column (TSK gel ODS-80TM) which equilibrated beforehand, it eluted in step WAIZU in the acetonitrile (pH2.0) 30% containing 0.01M hydrochloric acid, 50%, and 100%, and the Pori L-lactic acid (whenever [condensation] 3-19) which is an elution fraction was obtained 100%. The mass analysis result of this

matter is shown in drawing 1.

[0016] Pori L-lactic acid makes an annular low condensate a subject, and the straight chain-like low condensate will be intermingled in this so that clearly from the regular fragment ion peak of this drawing. It is surmised that an annular low condensate is the following chemical structure type.

[0017]

[Formula 1]



[0018] Neutralization processing of the Pori L-lactic acid obtained in the example for injection of the example of pharmaceutical preparation above-mentioned manufacture was carried out by 1-N sodium hydroxide, after dissolving in the 70-80-degree C method propylene glycol of an office and carrying out filtration sterilization of what carried out reduced pressure drying with 0.45-micrometer filter so that it may become 100mg [ml] concentration, in sterile, it poured distributively, and filled up the vial bottle with 15ml at a time, and injections were prepared.

[0019] Like the example above for taking orally of pharmaceutical preparation, neutralization processing of the Pori L-lactic acid obtained in the example of manufacture was carried out by 1-N sodium hydroxide, in addition, what carried out reduced pressure drying was mixed so that 250mg might be contained in sorbitol 1g, and the powder material for taking orally was prepared.

[0020] In order to check the safety of toxic experiment 1 Pori L-lactic acid, the intravenous injection of 15, 30, and 60 mg/kg was carried out to the male ICR system mouse for two weeks every day. The death during an administration period did not have any administration group, the action including motion cooperativeness, defecation, and urination and change of a body condition were not accepted, but weight also changed favorably, and the range of the body weight gain in an administration period was 14.4-14.9g in low and by the high-dose group to 14.6g of a solvent control group.

[0021] Supposing clinical application (intravenous drip) in two toxic experiments, the Japan Braille Library drop intravenous injection (a part for about 60-drop/) of 40 mg/kg of Pori L-lactic acid was carried out to two dogs 15 whole days, and the safety was evaluated. There were not an abnormality symptom in an administration period and death, and its body conditions, such as temperature and a heart rate, were also normal. The opinion a hemology-inspection value also suggests ischemia, inflammation or a liver function, and renal dysfunction in a normal range, saying was not accepted, but it was checked that many organs and an organization do not have a lesion pathologically. The measurement result of main items is shown in a table 1.

[A table 1]

主要な測定項目	開始前	15日間点滴静注後
体重(kg)	13.0~16.0	15.0~17.5
赤血球数(万/立方mm)	497~523	453~483
ヘモグロビン量(g/dl)	12.8~13.0	13.1~13.9
白血球数(千/立方mm)	9.1~12.8	10.6~11.3
血小板数(万/立方mm)	14.3~15.6	10.5~11.3
GPT活性(U/l)	15~23	17~26
GOT活性(U/l)	29~45	24~43
BUN量(mg/dl)	14~32	14~17

[0022] In order to check the safety by toxic experiment 3 internal use, single time internal use of 2000 mg/kg which is the amounts of Pori L-lactic acid which can be maximum prescribed for the patient was carried out at the ICR system mouse of a sex, and it observed for two weeks. There are not an abnormality symptom after administration and generating of death, and the lethal dose by internal use was presumed to be a thing exceeding 2000 mg/kg. The weight of an administration mouse changed like the solvent control group, and the gross lesion was not accepted in the autopsy.

[0023] immunity activation and a cancer transition control experiment B16 melanoma transplantation mouse -- Pori L-lactic acid -- taking orally during seven days (500 mg/kg) -- or the intravenous injection (10 mg/kg) was carried out and NK activity (cancer cell injury activity of a spontaneous killer cell) was measured at the time of administration initiation and termination. Consequently, with the cancer-bearing mouse of contrast, to NK activity falling to 30% at the time of administration initiation, lowering of NK activity was not accepted but suppressing lowering of the immunological competence by cancer growth was checked by taking orally and the intravenous administration group of Pori L-lactic acid. The cancer colony count transferred to lungs in connection with this also decreased as compared with the control group.

[0024] Internal use (500 mg/kgx2) or subcutaneous injection (10 mg/kg) of the Pori L-lactic acid was carried out twice to the mouse which carried out intraperitoneal injection of the painkilling experiment acetic acid once, and the number of pain (agony) reactions induced with an acetic acid was measured. The number of pain (agony) reactions decreased by administration of Pori L-lactic acid, especially it decreased to 52% of the control group by the subcutaneous injection group, and the Tsuguaki analgesic effect was accepted.

[0025] 50 mg/kg of Pori L-lactic acid was administered orally to the mouse which suffered a loss in an antioncogene (p53) with oncogenesis prevention experiment gene modification technology over 3 times per week, and 20 weeks, and the rate of cancerogenesis and the death rate were evaluated. At the control group, cancer death began to occur and it increased from the 8th week gradually after that, and 20 weeks after, to having been survival of only one example (10%) among ten examples, by the Pori L-lactic acid administration group, the survival rate of 20 weeks after is 50%, and it was suggested that there are cancerogenesis prevention and the prolongation-of-life effectiveness.

[0026] the effect affect the energy metabolism of a cancer cell -- by the tumor cell increased actively, since it was dependent on the anaerobic glycolysis system in order to maintain energy supply of a large quantity, the effectiveness of Pori L-lactic acid over the pyruvate kinase and lactate dehydrogenase which are the key enzyme was examined. Pori L-lactic acid is in. Checking the pyruvate kinase and lactate dehydrogenase activity of FM3A ascites tumor cell supernatant liquid of the mouse breast cancer origin to Tsuguaki by vitro, in the case of the pyruvate kinase, in the case of 4mg [ml] /and lactate dehydrogenase, 50% activity inhibition concentration was 2.5mg/ml. It became clear that especially the lactate dehydrogenase activity of an FM3A ascites tumor cell was strongly prevented from the lactate dehydrogenase activity of normal rabbit muscles. On the other hand, by measurement of an anaerobic

glycolysis system, the amount of lactic-acid generation fell to 50% by 8mg [/ml] concentration of Pori L-lactic acid. The effect of the Pori L-lactic acid exerted on a pyruvate kinase and a lactate dehydrogenase activity list at an anaerobic glycolysis system is shown in drawing 2 , drawing 3 , and drawing 4 .

[0027] It was proved also in cytomorphology that the depression of a cancer cell or growth control might take place by inhibition of such glycolytic pathways. Namely, In vitro (culture) and in vivo (mouse intraperitoneal transplantation), When Pori L-lactic acid was applied to the FM3A ascites tumor cell of vivo (mouse intraperitoneal transplantation), the denaturation opinions on disappearance of a cytoplasm projection of a cancer cell, the reduction of plumping and chromatin with a remarkable nucleus, the vacuolation of cytoplasm, etc. or the opinion which suggests apoptosis was accepted. Furthermore, with the mouse which carried out intraperitoneal injection of the FM3A ascites tumor cell by every other day in 4mg/animal of Pori L-lactic acid after intraperitoneal transplantation, general status was good and the prolongation-of-life effectiveness which reaches by 2.5 times [twice / about / to] the life time (14 - 16 days) of a contrast mouse was accepted. [0028] In the case where Pori L-lactic acid is added and cultivated into the culture Homo sapiens colon cancer DLD1 and Homo sapiens gastric cancer AZ521 cell, the MTT activity after 72-hour exposure fell to 7 - 12% of the contrast with 47 - 48% of contrast by 1.9mg [/ml] concentration by 7.5mg [/ml] concentration, and the clear growth control activity which coincided with the inhibition effectiveness of glycolytic pathway was checked. The effect of the Pori L-lactic acid exerted on a culture Homo sapiens cancer cell (MTT activity) is shown in a table 2.

[A table 2]

試 験 群	ヒト胃癌AZ521		ヒト結腸癌DLD1	
	MTT活性	(%)	MTT活性	(%)
24時間曝露				
対照 (n=21)	0.714±0.063	(100)	0.615±0.061	(100)
ポリ乳酸				
1.9 mg/ml (n=6)	0.675±0.076	(96)	0.278±0.050	(45)
7.5 mg/ml (n=6)	0.030±0.0003	(4)	0.175±0.018	(28)
72時間曝露				
対照 (n=36)	0.276±0.024	(100)	0.239±0.028	(100)
ポリ乳酸				
1.9 mg/ml (n=6)	0.132±0.011	(48)	0.113±0.030	(47)
7.5 mg/ml (n=6)	0.020±0.004	(7)	0.028±0.005	(12)

[0029] Based on acceptance and request of a patient, a family, etc., the anticancer therapy by the intravenous drip of the Pori L-lactic acid injections prepared in the example 1 of pharmaceutical preparation was enforced for about 50 serious patients by whom the terminal cancer by the intravenous drip for which an operation cannot be clinical treatment undergone, postoperative ***** and metastatic cancer, and recurrent carcinoma are looked at. The standard therapy made the Pori L-lactic acid 2000mg/person/day intravenous drip during 20 days one period of treatment, in the intravenous drip, carried out the mixed dissolution and applied the 20ml [/day] injections concerned to 500ml (grape-sugar liquid, electrolyte liquid, xylitol) of infusion solutions.

[0030] Among various kinds of primary carcinomas treated by Pori L-lactic acid injections, to colon cancer, an esophagus cancer, and a breast cancer, the most remarkable growth depressor effect was accepted and it became clear that the metastatic cancer to a recurrence and brain of such cancers, bone marrow, etc. was also controlled. To ***** especially looked at by the cancer patient immediately after the therapy by radiotherapy or the surgical extirpation way (about 14 persons), the anticancer

effectiveness was Tsuguaki, the improvement was accepted by 70 - 80% of the patient, among these eight persons were judged to be what recovered mostly clinically. Furthermore, in these injections, recovery from subjective signs, such as an improvement of not only the clear antitumor effectiveness but a nutrition and an ischemia condition and malaise, is remarkable, and that reduction and the impaired liver function of a white blood cell count which are radiotherapy and the side effect of anticancer agent administration were recovered at an early stage is change which should be mentioned specially, and it has suggested that the high anticancer effectiveness is expectable with concomitant use with the existing cure.

[0031] The side effect of Pori L-lactic acid is not accepted substantially, but when an intravenous drip is carried out on the 2000mgx2-/day which corresponds the twice of a standard dose, and also when an intravenous drip is carried out continuously for a long period of time (for about three months) every day, it has not generated and special abnormalities can be said to be very high [safety]. Although it might generate heat transient as a change peculiar to a cancer patient which is not generated in healthy people especially at the time of a first-time intravenous drip, it was slight, and a time was used together in 100-200mg /of Saxizon (succinic-acid DEHIDORO cortisone) in order to remove a patient's anxiety, and it was a request.

[0032] Case 1: Although there is infestation colon cancer accompanied by seepage and adhesion with the colon cancer pancreas and the surgical resection way and the by-pass operation were performed, the intravenous drip of these injections by the standard therapy of the rear-spring-supporter above was performed to the 60-year-old man by whom ***** was looked at, without complete excision being impossible in about two years. Consequently, while growth control of cancer was checked by the X-ray or the ultrasonic echo, the clear depressor effect of transition of cancer and a recurrence was accepted. Furthermore, the improvement of the nutriture by relief of body symptoms, such as a pain, malaise, a feeling of *****, and nausea, appetite recovery, and the increment in weight was accepted after therapy initiation as characteristic change by these injections in about three days - ten days, energy got over in connection with this, it was released also from mental anxiety or a mental decay condition, and the improvement in life activity was found.

[0033] Case 2: The metastatic cancer of the extensive nature to lungs was discovered after the surgical resection of the lung metastasis cancer colon cancer of colon cancer, and the therapy by the same intravenous drip was given to the 60-year-old man judged to be life-expectancy three - four months by the shape of atelectasis. Although shading of lungs remained, through the therapy period for about three years, the lung function was very good, there is no transition to the amplification opinion and other organs of a cancer disease blow hole, and the remarkable prolongation-of-life effectiveness was accepted. Life activity was in the almost normal condition, without appetite and the nutriture having been good and being accompanied by body symptoms, such as a pain, also by this example.

[0034] Case 3: By the male of 50 years old of carrier beams, hematemesis took place the surgical resection which contains total gastrectomy for an esophagus cancer esophagus cancer the 17 months after, it appealed against anorexia and dysphagia, and the same intravenous drip was given to the patient concerned by whom a recurrence nature esophagus cancer (about 6cm) and a constriction were discovered by the anastomosis section of operative surgery by endoscopy. A food intake will become possible after therapy initiation in ten days, also endoscopically cutback-izing of cancer and Bahnung of an alimentary canal are checked, and the condition also with subsequent good followup is maintained.

[0035] Case 4: It appealed against the pain of an innominate bone and a rib after the operation of milk cancer-juice cancer in 3rd, and to the 42-year-old woman by whom metastatic cancer was discovered by the bone sintigram, the intravenous drip of these injections was carried out similarly, and they were treated. This patient is undergoing the therapy of an anticancer agent over [after cancer discovery] four months, and reduction (2,900), ischemia opinion (the number of red cell 3,840,000, hemoglobin value 10.7 g/dl), and hepatopathy (GPT value 102U) of a white blood cell count were accepted in the inspection at the time of therapy initiation. There will be recovery (8,100) of a white blood cell count, ischemia, and an improvement (GPT value 21U) of a liver function after intravenous-drip initiation on the 4th, and subjective signs, such as malaise, pectoralgia, and ostealgia, disappeared on the 7th. The

intravenous drip of one period of treatment is ended, it is changing that there is no subjective sign also at the event after two-year progress, and control or a halt of metastatic cancer growth is checked. To the cancer of a gynecology system, the inclination for the effectiveness of these injections to be comparatively high is shown, and there are comparatively many long-term survival or examples of higher efficacy. Generally, since the sense of incongruity of a cancer part was sued for the milk cancer patient at the time of an intravenous drip, the direct operation over cancer heard, and it was also proved that cancer local remedy, such as *****, was one of the useful application paths of these injections.

[0036] Although it was expected from the metabolic turnover and physiological functions of short chain fatty acid, such as a lactic acid, the improvement effect which receives unusually [sugar and lipid metabolism] was also suggested, and the sugar in the opinions on the diabetes mellitus which joined for this clinical example, hyperlipidemia, etc., i.e., the blood serum which went up, and urine, serum cholesterol, and a triglyceride value were recovered normally. These combined with the liver function improvement effect of these injections etc., and were considered to act in favor of the improvement of a malignant tumor. Moreover, as a result of trying concomitant use with an intravenous drip and the powder material for taking orally prepared in the example 2 of pharmaceutical preparation, the useful thing became clear to the maintenance and enhancement of effectiveness by these injections.

[0037] Liver transition is discovered by the extraction of the example breast cancer of clinical treatment by internal use, the powder material for taking orally prepared in the example 2 of pharmaceutical preparation is prescribed to the female patient pronounced more as life-expectancy three months impossible [an operation], and a day is [continuation] under intake to him in about 8g (about 2400mg/ (day) as Pori L-lactic acid) /. For seven months which will be poured, by the inspection after intake, there is an uptrend of the condition which can fulfill an improvement of a liver function and duties, and clear growth control and the prolongation-of-life effectiveness of cancer are checked.

[0038]

[Effect of the Invention] While especially this invention shows the growth control in which the Pori L-lactic acid of 3-19 was [whenever / condensation] excellent to colon cancer, an esophagus cancer, and a breast cancer, transition and a recurrence of such cancers are controlled, it shows clearly that it has a remarkable condition improvement operation, and the intravenous drip of the matter concerned added to the infusion solution etc. shows that it can become an effective cure to these malignant tumors. Since the Pori L-lactic acid concerned is the low condensation product of the L-lactic acid originating in a biogenic substance, biocompatibility is very high and the severest intravascular injection or a side effect is the description that it is big a thing equal [that there is nothing] and a thing [list / hypodermically or an oral path / the antitumor effectiveness]. While it can apply also in the state of a patient with difficult each phase from the early stages of a stadium to [from such a property] the last stage and treatment and the greatest curative effect can be expected, combining the existing antitumor therapy suitably, it makes it possible to mitigate or remove the side effect by the existing anticancer therapies, such as reduction in a leucocyte, and an impaired liver function. Furthermore, the oncogenesis prevention which closes if, and was suggested [insurance and] experimentally can be presented with prolonged continuous intake. It was proved that the improvement operation of an immunity activation operation, the liver function centering on a glycolipid metabolic turnover, and a digestive function related to the antitumor effectiveness of Pori L-lactic acid. Furthermore, although it depended for the cancer with a large proliferation rate to glycolysis ability strongly in order unlike a normal cell metabolic activity or energy demand nature is very high and to maintain this, it became clear that cancer growth depressor effect could therefore be demonstrated for Pori L-lactic acid to control the anaerobic glycolysis system of such cancer. Especially, to the lactate dehydrogenase activity of the cancer cell origin, inhibition is strong and has suggested possibility of being one of the operation **** of Pori L-lactic acid. Unlike the existing anticancer drug which shows a powerful cell injury operation, these operations are imagined to be those from which Pori L-lactic acid is the cause which shows a comparatively large anticancer spectrum, without being accompanied by the critical side effect. It became clear that there was an improvement effect which was excellent in the clinical experience to the lowering of life activity which needs body symptoms, such as malnutrition containing anorexia and a loss weight, ischemia and a pain, and malaise,

and mental and corporal care. There is an operation which improves remarkably the depression of the appetite it is of a poor appetite to a lifting and the clincher of death in lowering of immunological competence and physical strength in a malignant tumor especially, or abolition, and it is mentioned as important effectiveness of this agent. Moreover, also in the therapy of an intractable disease including the relaxation therapy and anti-acquired immunodeficiency syndrome therapy of the cachexia accompanying a chronic disease, it has a big meaning. Thus, Pori L-lactic acid has simultaneously the operation which only improves the accessory symptom of not only the anticancer effectiveness but a malignant tumor, and becoming an effective means for aiming at improvement in the quality (QOL) of a life of a patient is shown, and it can be said to be what sees synthetically and exceeds the existing anticancer drug.

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[0006]

[Translation done.]

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EFFECT OF THE INVENTION

[Effect of the Invention] While especially this invention shows the growth control in which the Pori L-lactic acid of 3-19 was [whenever / condensation] excellent to colon cancer, an esophagus cancer, and a breast cancer, transition and a recurrence of such cancers are controlled, it shows clearly that it has a remarkable condition improvement operation, and the intravenous drip of the matter concerned added to the infusion solution etc. shows that it can become an effective cure to these malignant tumors. Since the Pori L-lactic acid concerned is the low condensation product of the L-lactic acid originating in a biogenic substance, biocompatibility is very high and the severest intravascular injection or a side effect is the description that it is big a thing equal [that there is nothing] and a thing [list / hypodermically or an oral path / the antitumor effectiveness]. While it can apply also in the state of a patient with difficult each phase from the early stages of a stadium to [from such a property] the last stage and treatment and the greatest curative effect can be expected, combining the existing antitumor therapy suitably, it makes it possible to mitigate or remove the side effect by the existing anticancer therapies, such as reduction in a leucocyte, and an impaired liver function. Furthermore, the oncogenesis prevention which closes if , and was suggested [insurance and] experimentally can be presented with prolonged continuous intake. It was proved that the improvement operation of an immunity activation operation, the liver function centering on a glycolipid metabolic turnover, and a digestive function related to the antitumor effectiveness of Pori L-lactic acid. Furthermore, although it depended for the cancer with a large proliferation rate to glycolysis ability strongly in order unlike a normal cell metabolic activity or energy demand nature is very high and to maintain this, it became clear that cancer growth depressor effect could therefore be demonstrated for Pori L-lactic acid to control the anaerobic glycolysis system of such cancer. Especially, to the lactate dehydrogenase activity of the cancer cell origin, inhibition is strong and has suggested possibility of being one of the operation **** of Pori L-lactic acid. Unlike the existing anticancer drug which shows a powerful cell injury operation, these operations are imagined to be those from which Pori L-lactic acid is the cause which shows a comparatively large anticancer spectrum, without being accompanied by the critical side effect. It became clear that there was an improvement effect which was excellent in the clinical experience to the lowering of life activity which needs body symptoms, such as malnutrition containing anorexia and a loss weight, ischemia and a pain, and malaise, and mental and corporal care. There is an operation which improves remarkably the depression of the appetite it is of a poor appetite to a lifting and the clincher of death in lowering of immunological competence and physical strength in a malignant tumor especially, or abolition, and it is mentioned as important effectiveness of this agent. Moreover, also in the therapy of an intractable disease including the relaxation therapy and anti-acquired immunodeficiency syndrome therapy of the cachexia accompanying a chronic disease, it has a big meaning. Thus, Pori L-lactic acid has simultaneously the operation which only improves the accessory symptom of not only the anticancer effectiveness but a malignant tumor, and becoming an effective means for aiming at improvement in the quality (QOL) of a life of a patient is shown, and it can be said to be what sees synthetically and exceeds the existing anticancer drug.

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MEANS

[Means for Solving the Problem] In order to attain the above-mentioned object, the anticancer drug of this invention Dehydration condensation of the L-lactic acid is carried out according to gradual reduced pressure and temperature up in nitrogen-gas-atmosphere mind. After carrying out reduced pressure drying of the obtained ethanol and methanol meltable component of reaction mixture, An opposite phase ODS column chromatography is performed. In 25 - 50% acetonitrile water solution of pH2.0 After elution, The mixed Pori L-lactic acid of the shape of annular [of 3-19] and a straight chain is used as a principal component whenever [condensation / which is the fraction eluted in 100% acetonitrile of pH2.0], and the anticancer drug used for the cancer chosen from colon cancer, an esophagus cancer, and a breast cancer is used.

[0010] Although Pori L-lactic acid consists of condensation products of the shape of annular and a straight chain, even if it compares with data, like that a kind of reversible equilibrium relation is materialized among both, and the antitumor effectiveness is discovered with compound of each fraction from which whenever [versatility / of the bioactive of Pori L-lactic acid / or condensation] differs, the meaning of carrying out mutual separation and using the condensation product of the shape of annular and a straight chain is scarce.

[0011] Separation purification of the Pori L-lactic acid of 3-19 is carried out whenever [condensation], and in order to present a actual activity, after carrying out alkali neutralization, use as original powder what carried out reduced pressure drying, and this is dissolved or suspended in sterile in a suitable solvent, and a vial bottle etc. is filled up with it so that it may become predetermined concentration, and let it be injections.

[0012] An oral agent mixes with a suitable dispersant, a basis, an allocated type agent, etc. said original powder processed similarly so that it may become predetermined concentration, and it pharmaceutical-preparation-izes it in the gestalt of powder material, a capsule, liquids and solutions, etc.

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EXAMPLE.

[Example]

put 500ml of L-lactic acid into the separable flask stored in the example mantle heater of manufacture, perform 300ml inflow for /and of nitrogen gas, and churning, and ***** should pass the top-down communication trunk which kept it warm -- while leading to a flask with a reflux condenser -- 145 degrees C -- 3 hours -- heating -- further -- after decompressing to 150mmHg(s) and heating for 3 hours, at 155 degrees C of 3mmHg, it heated at 185 degrees C of 3mmHg(s) at the last for 1.5 hours, and the Pori L-lactic acid which is a resultant was obtained for 3 hours.

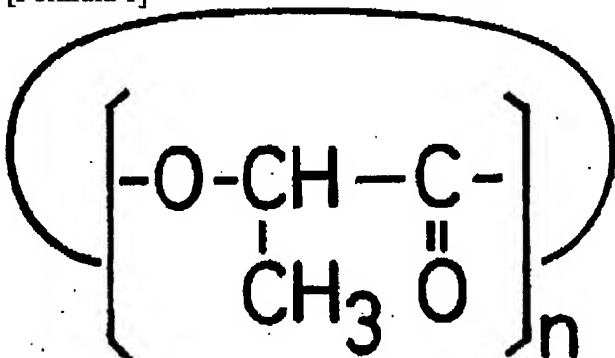
[0014] after keeping the obtained Pori L-lactic acid at 100 degrees C and dropping methanol 400ml following ethanol 100ml, respectively -- cooling radiationally -- this -- further -- methanol 500ml -- it agitated [be / it / under adding] well, and after putting, it filtered and refined and reduced pressure drying of the filtrate was carried out, it dissolved in the acetonitrile and the whole quantity was set to 200ml (undiluted solution).

[0015] The aforementioned undiluted solution was covered over the opposite phase ODS column (TSK gel ODS-80TM) which equilibrated beforehand, it eluted in step WAIZU in the acetonitrile (pH2.0) 30% containing 0.01M hydrochloric acid, 50%, and 100%, and the Pori L-lactic acid (whenever [condensation] 3-19) which is an elution fraction was obtained 100%. The mass analysis result of this matter is shown in drawing 1.

[0016] Pori L-lactic acid makes an annular low condensate a subject, and the straight chain-like low condensate will be intermingled in this so that clearly from the regular fragment ion peak of this drawing. It is surmised that an annular low condensate is the following chemical structure type.

[0017]

[Formula 1]



[0018] Neutralization processing of the Pori L-lactic acid obtained in the example for injection of the example of pharmaceutical preparation above-mentioned manufacture was carried out by 1-N sodium hydroxide, after dissolving in the 70-80-degree C method propylene glycol of an office and carrying out filtration sterilization of what carried out reduced pressure drying with 0.45-micrometer filter so that it may become 100mg [/ml] concentration, in sterile, it poured distributively, and filled up the vial bottle

with 15ml at a time, and injections were prepared.

[0019] Like the example above for taking orally of pharmaceutical preparation, neutralization processing of the Pori L-lactic acid obtained in the example of manufacture was carried out by 1-N sodium hydroxide, in addition, what carried out reduced pressure drying was mixed so that 250mg might be contained in sorbitol 1g, and the powder material for taking orally was prepared.

[0020] In order to check the safety of toxic experiment 1 Pori L-lactic acid, the intravenous injection of 15, 30, and 60 mg/kg was carried out to the male ICR system mouse for two weeks every day. The death during an administration period did not have any administration group, the action including motion cooperativeness, defecation, and urination and change of a body condition were not accepted, but weight also changed favorably, and the range of the body weight gain in an administration period was 14.4-14.9g in low and by the high-dose group to 14.6g of a solvent control group.

[0021] Supposing clinical application (intravenous drip) in two toxic experiments, the Japan Braille Library drop intravenous injection (a part for about 60-drop/) of 40 mg/kg of Pori L-lactic acid was carried out to two dogs 15 whole days, and the safety was evaluated. There were not an abnormality symptom in an administration period and death, and its body conditions, such as temperature and a heart rate, were also normal. The opinion a hemology-inspection value also suggests ischemia, inflammation or a liver function, and renal dysfunction in a normal range, saying was not accepted, but it was checked that many organs and an organization do not have a lesion pathologically. The measurement result of main items is shown in a table 1.

[A table 1]

主要な測定項目	開始前	15日間点滴静注後
体重(kg)	13.0~16.0	15.0~17.5
赤血球数(万/立方mm)	497~523	453~483
ヘモグロビン量(g/dl)	12.8~13.0	13.1~13.9
白血球数(千/立方mm)	9.1~12.8	10.6~11.3
血小板数(万/立方mm)	14.3~15.6	10.5~11.3
GPT活性(U/l)	15~23	17~26
GOT活性(U/l)	29~45	24~43
BUN量(mg/dl)	14~32	14~17

[0022] In order to check the safety by toxic experiment 3 internal use, single time internal use of 2000 mg/kg which is the amounts of Pori L-lactic acid which can be maximum prescribed for the patient was carried out at the ICR system mouse of a sex, and it observed for two weeks. There are not an abnormality symptom after administration and generating of death, and the lethal dose by internal use was presumed to be a thing exceeding 2000 mg/kg. The weight of an administration mouse changed like the solvent control group, and the gross lesion was not accepted in the autopsy.

[0023] immunity activation and a cancer transition control experiment B16 melanoma transplantation mouse -- Pori L-lactic acid -- taking orally during seven days (500 mg/kg) -- or the intravenous injection (10 mg/kg) was carried out and NK activity (cancer cell injury activity of a spontaneous killer cell) was measured at the time of administration initiation and termination. Consequently, with the cancer-bearing mouse of contrast, to NK activity falling to 30% at the time of administration initiation, lowering of NK activity was not accepted but suppressing lowering of the immunological competence by cancer growth was checked by taking orally and the intravenous administration group of Pori L-lactic acid. The cancer colony count transferred to lungs in connection with this also decreased as compared with the control group.

[0024] Internal use (500 mg/kgx2) or subcutaneous injection (10 mg/kg) of the Pori L-lactic acid was carried out twice to the mouse which carried out intraperitoneal injection of the painkilling experiment

acetic acid once, and the number of pain (agony) reactions induced with an acetic acid was measured. The number of pain (agony) reactions decreased by administration of Pori L-lactic acid, especially it decreased to 52% of the control group by the subcutaneous injection group, and the Tsuguaki analgesic effect was accepted.

[0025] 50 mg/kg of Pori L-lactic acid was administered orally to the mouse which suffered a loss in an antioncogene (p53) with oncogenesis prevention experiment gene modification technology over 3 times per week, and 20 weeks, and the rate of cancerogenesis and the death rate were evaluated. At the control group, cancer death began to occur and it increased from the 8th week gradually after that, and 20 weeks after, to having been survival of only one example (10%) among ten examples, by the Pori L-lactic acid administration group, the survival rate of 20 weeks after is 50%, and it was suggested that there are cancerogenesis prevention and the prolongation-of-life effectiveness.

[0026] the effect affect the energy metabolism of a cancer cell – by the tumor cell increased actively, since it was dependent on the anaerobic glycolysis system in order to maintain energy supply of a large quantity, the effectiveness of Pori L-lactic acid over the pyruvate kinase and lactate dehydrogenase which are the key enzyme was examined. Pori L-lactic acid is in. Checking the pyruvate kinase and lactate dehydrogenase activity of FM3A ascites tumor cell supernatant liquid of the mouse breast cancer origin to Tsuguaki by vitro, in the case of the pyruvate kinase, in the case of 4mg [ml] /and lactate dehydrogenase, 50% activity inhibition concentration was 2.5mg/ml. It became clear that especially the lactate dehydrogenase activity of an FM3A ascites tumor cell was strongly prevented from the lactate dehydrogenase activity of normal rabbit muscles. On the other hand, by measurement of an anaerobic glycolysis system, the amount of lactic-acid generation fell to 50% by 8mg [/ml] concentration of Pori L-lactic acid. The effect of the Pori L-lactic acid exerted on a pyruvate kinase and a lactate dehydrogenase activity list at an anaerobic glycolysis system is shown in drawing 2 , drawing 3 , and drawing 4 .

[0027] It was proved also in cytomorphology that the depression of a cancer cell or growth control might take place by inhibition of such glycolytic pathways. Namely, In vitro (culture) and in When Pori L-lactic acid was applied to the FM3A ascites tumor cell of vivo (mouse intraperitoneal transplantation), the denaturation opinions on disappearance of a cytoplasm projection of a cancer cell, the reduction of plumping and chromatin with a remarkable nucleus, the vacuol ation of cytoplasm, etc. or the opinion which suggests apoptosis was accepted. Furthermore, with the mouse which carried out intraperitoneal injection of the FM3A ascites tumor cell by every other day in 4mg/animal of Pori L-lactic acid after intraperitoneal transplantation, general status was good and the prolongation-of-life effectiveness which reaches by 2.5 times [twice / about / to] the life time (14 - 16 days) of a contrast mouse was accepted.

[0028] In the case where Pori L-lactic acid is added and cultivated into the culture Homo sapiens colon cancer DLD1 and Homo sapiens gastric cancer AZ521 cell, the MTT activity after 72-hour exposure fell to 7 - 12% of the contrast with 47 - 48% of contrast by 1.9mg [/ml] concentration by 7.5mg [/ml] concentration, and the clear growth control activity which coincided with the inhibition effectiveness of glycolytic pathway was checked. The effect of the Pori L-lactic acid exerted on a culture Homo sapiens cancer cell (MTT activity) is shown in a table 2.

[A table 2]

試 験 群	ヒト胃癌AZ251		ヒト結腸癌DLD1	
	MTT活性	(%)	MTT活性	(%)
24時間曝露				
対照 (n=21)	0.714±0.063	(100)	0.615±0.061	(100)
ポリ乳酸				
1.9 mg/ml (n=6)	0.675±0.076	(96)	0.278±0.050	(45)
7.5 mg/ml (n=6)	0.030±0.0003	(4)	0.175±0.018	(28)
72時間曝露				
対照 (n=36)	0.276±0.024	(100)	0.239±0.026	(100)
ポリ乳酸				
1.9 mg/ml (n=6)	0.132±0.011	(48)	0.113±0.030	(47)
7.5 mg/ml (n=6)	0.020±0.004	(7)	0.028±0.005	(12)

[0029] Based on acceptance and request of a patient, a family, etc., the anticancer therapy by the intravenous drip of the Pori L-lactic acid injections prepared in the example 1 of pharmaceutical preparation was enforced for about 50 serious patients by whom the terminal cancer by the intravenous drip for which an operation cannot be clinical treatment undergone, postoperative ***** and metastatic cancer, and recurrent carcinoma are looked at. The standard therapy made the Pori L-lactic acid 2000mg/person/day intravenous drip during 20 days one period of treatment, in the intravenous drip, carried out the mixed dissolution and applied the 20ml [/day] injections concerned to 500ml (grape-sugar liquid, electrolyte liquid, xylitol) of infusion solutions.

[0030] Among various kinds of primary carcinomas treated by Pori L-lactic acid injections, to colon cancer, an esophagus cancer, and a breast cancer, the most remarkable growth depressor effect was accepted and it became clear that the metastatic cancer to a recurrence and brain of such cancers, bone marrow, etc. was also controlled. To ***** especially looked at by the cancer patient immediately after the therapy by radiotherapy or the surgical extirpation way (about 14 persons), the anticancer effectiveness was Tsuguaki, the improvement was accepted by 70 - 80% of the patient, among these eight persons were judged to be what recovered mostly clinically. Furthermore, in these injections, recovery from subjective signs, such as an improvement of not only the clear antitumor effectiveness but a nutrition and an ischemia condition and malaise, is remarkable, and that reduction and the impaired liver function of a white blood cell count which are radiotherapy and the side effect of anticancer agent administration were recovered at an early stage is change which should be mentioned specially, and it has suggested that the high anticancer effectiveness is expectable with concomitant use with the existing cure.

[0031] The side effect of Pori L-lactic acid is not accepted substantially, but when an intravenous drip is carried out on the 2000mgx2-/day which corresponds the twice of a standard dose, and also when an intravenous drip is carried out continuously for a long period of time (for about three months) every day, it has not generated and special abnormalities can be said to be very high [safety]. Although it might generate heat transient as a change peculiar to a cancer patient which is not generated in healthy people especially at the time of a first-time intravenous drip, it was slight, and a time was used together in 100-200mg /of Saxizon (succinic-acid DEHIDORO cortisone) in order to remove a patient's anxiety, and it was a request.

[0032] Case 1: Although there is infestation colon cancer accompanied by seepage and adhesion with the colon cancer pancreas and the surgical resection way and the by-pass operation were performed, the intravenous drip of these injections by the standard therapy of the rear-spring-supporter above was performed to the 60-year-old man by whom ***** was looked at, without complete excision being

impossible in about two years. Consequently, while growth control of cancer was checked by the X-ray or the ultrasonic echo, the clear depressor effect of transition of cancer and a recurrence was accepted. Furthermore, the improvement of the nutriture by relief of body symptoms, such as a pain, malaise, a feeling of *****, and nausea, appetite recovery, and the increment in weight was accepted after therapy initiation as characteristic change by these injections in about three days - ten days, energy got over in connection with this, it was released also from mental anxiety or a mental decay condition, and the improvement in life activity was found.

[0033] Case 2: The metastatic cancer of the extensive nature to lungs was discovered after the surgical resection of the lung metastasis cancer colon cancer of colon cancer, and the therapy by the same intravenous drip was given to the 60-year-old man judged to be life-expectancy three - four months by the shape of atelectasis. Although shading of lungs remained, through the therapy period for about three years, the lung function was very good, there is no transition to the amplification opinion and other organs of a cancer disease blow hole, and the remarkable prolongation-of-life effectiveness was accepted. Life activity was in the almost normal condition, without appetite and the nutriture having been good and being accompanied by body symptoms, such as a pain, also by this example.

[0034] Case 3: By the male of 50 years old of carrier beams, hematemesis took place the surgical resection which contains total gastrectomy for an esophagus cancer esophagus cancer the 17 months after, it appealed against anorexia and dysphagia, and the same intravenous drip was given to the patient concerned by whom a recurrence nature esophagus cancer (about 6cm) and a constriction were discovered by the anastomosis section of operative surgery by endoscopy. A food intake will become possible after therapy initiation in ten days, also endoscopically cutback-izing of cancer and Bahnung of an alimentary canal are checked, and the condition also with subsequent good followup is maintained.

[0035] Case 4: It appealed against the pain of an innominate bone and a rib after the operation of milk cancer-juice cancer in 3rd, and to the 42-year-old woman by whom metastatic cancer was discovered by the bone sintigram, the intravenous drip of these injections was carried out similarly, and they were treated. This patient is undergoing the therapy of an anticancer agent over [after cancer discovery] four months, and reduction (2,900), ischemia opinion (the number of red cell 3,840,000, hemoglobin value 10.7 g/dl), and hepatopathy (GPT value 102U) of a white blood cell count were accepted in the inspection at the time of therapy initiation. There will be recovery (8,100) of a white blood cell count, ischemia, and an improvement (GPT value 21U) of a liver function after intravenous-drip initiation on the 4th, and subjective signs, such as malaise, pectoralgia, and ostealgia, disappeared on the 7th. The intravenous drip of one period of treatment is ended, it is changing that there is no subjective sign also at the event after two-year progress, and control or a halt of metastatic cancer growth is checked. To the cancer of a gynecology system, the inclination for the effectiveness of these injections to be comparatively high is shown, and there are comparatively many long-term survival or examples of higher efficacy. Generally, since the sense of incongruity of a cancer part was sued for the milk cancer patient at the time of an intravenous drip, the direct operation over cancer heard, and it was also proved that cancer local remedy, such as *****, was one of the useful application paths of these injections.

[0036] Although it was expected from the metabolic turnover and physiological functions of short chain fatty acid, such as a lactic acid, the improvement effect which receives unusually [sugar and lipid metabolism] was also suggested, and the sugar in the opinions on the diabetes mellitus which joined for this clinical example, hyperlipidemia, etc., i.e., the blood serum which went up, and urine, serum cholesterol, and a triglyceride value were recovered normally. These combined with the liver function improvement effect of these injections etc., and were considered to act in favor of the improvement of a malignant tumor. Moreover, as a result of trying concomitant use with an intravenous drip and the powder material for taking orally prepared in the example 2 of pharmaceutical preparation, the useful thing became clear to the maintenance and enhancement of effectiveness by these injections.

[0037] Liver transition is discovered by the extraction of the example breast cancer of clinical treatment by internal use, the powder material for taking orally prepared in the example 2 of pharmaceutical preparation is prescribed to the female patient pronounced more as life-expectancy three months impossible [an operation], and a day is [continuation] under intake to him in about 8g (about 2400mg/

(day) as Pori L-lactic acid) /. For seven months which will be poured, by the inspection after intake, there is an uptrend of the condition which can fulfill an improvement of a liver function and duties, and clear growth control and the prolongation-of-life effectiveness of cancer are checked.

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DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]

[Drawing 1] The mass spectrum diagram of the Pori L-lactic acid obtained in the example of manufacture of this invention.

[Drawing 2] Effectiveness of Pori L-lactic acid exerted on the pyruvate kinase activity (O) of the FM3A ascites tumor cell origin, and the pyruvate kinase activity (**) of the normal rabbit muscular origin. An axis of ordinate makes 100% activity in case Pori L-lactic acid does not exist, and shows activity in case the Pori L-lactic acid of the concentration shown on an axis of abscissa exists as relative activity.

[Drawing 3] Effectiveness of Pori L-lactic acid exerted on the lactate dehydrogenase activity (O) of the FM3A ascites tumor cell origin, and the lactate dehydrogenase activity (**) of the normal rabbit muscular origin. An axis of ordinate makes 100% activity in case Pori L-lactic acid does not exist, and shows activity in case the Pori L-lactic acid of the concentration shown on an axis of abscissa exists as relative activity.

[Drawing 4] Effectiveness of Pori L-lactic acid exerted on the anaerobic glycolysis system in FM3A ascites tumor cell supernatant liquid. Under the conditions which carried out the nitrogen purge of the air, the amount of lactic-acid generation in case Pori L-lactic acid does not exist was made into 100%, and the amount of generation of the lactic acid from the glucose by FM3A ascites tumor cell supernatant liquid was measured.

[Translation done.]